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EXAMINER	
CAPPS, KEVIN J	

ART UNIT	PAPER NUMBER
1617	

DATE MAILED: 07/28/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/508,336	BIRCH ET AL.	
	Examiner	Art Unit	
	Kevin J. Capps	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 May 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-16,19,38,39,41 and 48-66* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-16,19,38,39,41 and 48-66* is/are rejected.

7)☒ Claim(s) *61* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *4/5/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of the Claims

1. This Office Action is in response to the Amendments and Remarks/Arguments filed on May 22, 2006. The amendment of claims 48 and 49, and addition of new claims 51-66 in the Amendments filed on May 22, 2006, is acknowledged. Claims 1-16, 19, 38, 39, 41, and 48-66 are pending and examined on the merits herein.

2. Because the priority papers for the instant application were filed at the International stage of filing, the requirements under 35 § USC 119 (a-d) for the claim of foreign priority have been fulfilled.

3. Applicant's adoption of the suggested title is acknowledged and the objection is accordingly withdrawn.

4. Claims 48-50 stand rejected under 35 § USC 102(b) as being anticipated by Eriksen et al. The rejection is maintained and restated to address the amendments and new claims 51 and 52. Applicant's arguments are addressed below.

5. Claims 1-15, 38-39, and 41 stand rejected under 35 § USC 103 as being unpatentable over Eriksen et al. in view of Watts et al., Reich et al., and Nairn. The rejection is maintained and Applicant's arguments are addressed below.

6. Claim 16 stands rejected under 35 § USC 103 as being unpatentable over Eriksen et al. in view of Koochaki. The rejection is maintained and restated to address the new claims 53-59. Applicant's arguments are addressed below.

7. Claim 19 stands rejected under 35 § USC 103 as being unpatentable over Eriksen et al. in view of Williams et al. The rejection is maintained and restated to address the new claims 60-66. Applicant's arguments are addressed below.

8. Applicant's have taken no action to resolve the provisional double-patenting rejections over co-pending application 10/508,315. Thus, the rejections are maintained until such action has been taken. The double-patenting rejection of claims 1, 13, 16, 19, 38, 39, and 41 over US Patent No. 6,387,917 is maintained. Applicant's arguments are addressed below. The double-patenting rejections are restated to address the amendments and new claims.

9. In view of Applicant's amendments to claims and addition of new claims, the following new rejections are also being made.

Information Disclosure Statement

10. The information disclosure statement (IDS) filed on April 5, 2006, is in compliance with the provisions of 37 § CFR 1.97. The payment of the fee under § 1.17(p) is acknowledged. Accordingly, the IDS is being considered by the Examiner.

Claim Objections

11. Claim 61 is objected to because of the following informalities: Claim 61 depends from claim 62. A claim should depend upon a preceding claim (MPEP § 608.01(n)). Appropriate correction is required.

Claim Rejections - 35 USC § 102

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

12. Claims 48-52 are rejected under 35 U.S.C. 102(b) as being anticipated by Eriksen et al. (Applicant-cited reference on IDS: Eriksen, J. et al. *J. Pharm. Pharmacol.* **1989**, *41*, 803-805.).

13. Eriksen et al. teach a pharmaceutical composition suitable for use as an analgesic which comprises buprenorphine and a delivery agent whereby, upon introduction into the nasal cavity, the buprenorphine is delivered to the bloodstream to produce within 0.5 to 20 minutes a plasma concentration of 0.4 ng/ml or greater, which is maintained for up to 6 hours (see "The spray-device and the buprenorphine-spray solution" and "Procedure" on pp. 803-4 and Table 3 on p. 804). "The spray-device and the buprenorphine-spray solution" on p. 803 teaches the composition comprising buprenorphine and a delivery agent. Table 3 teaches plasma concentrations of buprenorphine after intranasal administration of the composition. Table 3 teaches a plasma concentration of 0.4 ng/ml or greater within 0.5 to 20 minutes after intranasal administration of the composition, and that this plasma concentration is maintained for up to 6 hours, and more specifically for 2-4 hours, after intranasal administration, thus anticipating the composition of claims 48 and 52.

14. Eriksen et al. also teach the method of inducing analgesia comprising intranasally administering said composition, and specifically the method wherein the dose of buprenorphine is 0.3 mg ("Procedure" section on pp. 803-4). Again, Table 3

teaches a plasma concentration of 0.4 ng/ml or greater within 0.5 to 20 minutes after intranasal administration of the composition, and that this plasma concentration is maintained for up to 6 hours, and more specifically for 2-4 hours, after intranasal administration of the composition, thus anticipating the method of claims 49-51.

Claim Rejections - 35 USC § 103

15. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

16. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

17. Claims 1-15, 38-39, and 41 are rejected under 35 U.S.C. 103(a) as being unpatentable over Eriksen et al. (Applicant-cited reference on IDS: Eriksen, J. et al. *J. Pharm. Pharmacol.* **1989**, *41*, 803-805.), in view of Watts et al. (Applicant-cited reference on IDS: WO 98/47535, October 29, 1998), Reich et al. (Reich, I., et al. "Tonicity, Osmoticity, Osmolality and Osmolarity" Remington: The Science and Practice or Pharmacy, Nineteenth Edition, Volume 1. Easton, PA: Mack, **1995**. pp. 613-615.),

and Nairn (Nairn, J. G. Solutions, Emulsions, Suspensions and Extracts" Remington: The Science and Practice or Pharmacy, Nineteenth Edition, Volume 2. Easton, PA: Mack, **1995**. p. 1502.).

18. Eriksen et al. teach an aqueous solution suitable for intranasal administration which comprises 2 mg/ml of buprenorphine or a physiologically acceptable salt or ester thereof, wherein the buprenorphine is buprenorphine hydrochloride. The composition of Eriksen et al. further comprises dextrose (see "The spray-device and the buprenorphine-spray solution" and "Procedure" on pp. 803-4). Due to the fact that Eriksen et al. do not add divalent metal cations into the composition during the preparation, it can be inferred that Eriksen et al. teach the composition as being substantially free of divalent metal cations.

19. Eriksen et al. also teach a method for the preparation of said composition ("The spray-device and the buprenorphine-spray solution" on p. 803).

20. Eriksen et al. teach a nasal delivery device loaded with said solution, wherein the nasal delivery device is a spray device ("The spray-device and the buprenorphine-spray solution" on p. 803).

21. Eriksen et al. do not teach the solutions as comprising pectin, wherein the pectin is at a concentration of 5-40 mg/ml, 10-30 mg/ml, or 10-40 mg/ml, and wherein the pectin has a degree of esterification of less than 50%, or a degree of esterification of from 10-35%. Eriksen et al. also do not teach the solution as having a pH of from 3-4.2 or from 3.5-4. Eriksen et al. do not teach the osmolality of the solution as being from 0.35 to 0.5 osmol/kg.

22. Watts et al. teach solutions which are substantially free of divalent metal ions and which comprise therapeutic agents and pectin with a low degree of esterification for administration intranasally, and specifically wherein the degree of esterification of pectin is less than 50%, and more preferably less than 35%, and further wherein the pectin is present at a concentration of from 1 to 100 mg/ml (p. 2, lines 23-26; p. 9, lines 22-27; p. 11, line 21 -p. 12, line 5; p. 12, lines 22-27; Example 1; claims 1-2). Watts et al. also teach that said solution has a pH from "2 to 9, more preferably from 3 to 8 and most preferably from 4-7." (p. 16, line 29 -p. 17, line 3). Watts et al. teach, "the lower the DE of the pectin, the lower the pH at which the composition will gel. pH may be adjusted in accordance with techniques which will be well known to those skilled in the art" (p. 17, lines 3-6). Thus, Watts et al. suggest optimizing the pH of the composition within the disclosed preferred ranges using routine experimentation based on the pectin that is incorporated into the composition.

23. Watts et al. also teach that the solutions comprising pectins and therapeutic agents should have a concentration of pectin greater than 4 mg/ml for solid gel formation upon intranasal administration (Example 1).

24. Nairn teaches that nasal solutions are usually isotonic (p. 1502).

25. Reich et al. teach, "The term isotonic, meaning equal tone, is in medical usage commonly used interchangeably with isoosmotic." (p. 613). Reich et al. also teach, "Serum osmolality often is stated loosely to be about 300 mOsmol/L." (p. 615).

26. Although the osmolality of the solution for intranasal administration of claim 11 of the current application is slightly higher than serum osmolality, this is necessitated by

the amount of pectin that is required by the teachings of Watts et al. in order that the solution gel upon intranasal administration (Example 1). Therefore, the osmolality of a solution for intranasal administration that comprises low DE pectin as the gelling agent should be close to isoosmotic and should have the required concentration of pectin to achieve gelling upon administration as taught by Narin, Reich et al., and Watts et al.

27. It would have been obvious to a person of ordinary skill in the art at the time of invention to incorporate pectins having a low degree of esterification into the solutions of Eriksen et al., to adjust the pH and osmolality of said solution to the appropriate ranges taught by Watts et al., to incorporate the solution into a spray device, and to intranasally deliver the solution in a method of inducing analgesia.

28. The person of ordinary skill in the art would have been motivated to introduce the gelling capacity taught by Watts et al. into the solutions of Eriksen et al. because this would improve the duration of the desired plasma concentration of the active agent delivered from the compositions in the method taught by Eriksen et al. by enhanced retention of the agent in the nasal cavity. As Watts et al. teach, "It would be most beneficial, due to ease of use and of administration, to have available a simple solution spray system that was suitable for the administration of drugs to the nose and, better still, for the drugs administered via such a system to have a long retention in the nasal cavity," (p. 2, lines 23-26). The person of ordinary skill in the art would have expected success absent evidence to the contrary.

29. Claims 16 and 53-59 are rejected under 35 U.S.C. 103(a) as being unpatentable over Eriksen et al. (Applicant-cited reference on IDS: Eriksen, J. et al. *J. Pharm. Pharmacol.* **1989**, *41*, 803-805.) in view of Koochaki (Applicant-cited reference on IDS: EP 0 571 671 A1).

30. Eriksen et al. teach the composition comprising dextrose and buprenorphine hydrochloride, as discussed above. The concentration of buprenorphine in the composition is 2 mg/ml, which is within the instantly claimed ranges. Eriksen et al. teach preparation of the composition and incorporation of said composition into a spray device for intranasal delivery ("The spray-device and the buprenorphine-spray solution" on p. 803). Eriksen et al. also teach a method of inducing analgesia comprising administering said composition intranasally ("Procedure" section on pp. 803-4).

31. Eriksen et al. do not teach the solutions as further comprising chitosan or hydroxypropylmethyl cellulose (HPMC), or as having a pH from 3 to 4.8.

32. Koochaki teaches a composition comprising a drug and a pharmaceutical carrier, wherein the carrier comprises a non-ionic cellulose ether, preferably HPMC, and a chitin-derived polymer, which may be chitosan (p. 2, lines 38-44; Example 1; Example 2; claims 1-3 and 6). Koochaki teaches that the compositions are "for application to the mucosa of the nasal cavity." (claim 1). Koochaki teaches a method of incorporating the HPMC and chitosan into a composition containing a drug and adjusting the pH to about 4.5 (Example 1).

33. It would have been obvious to a person of ordinary skill in the art at the time of invention to modify the procedure for preparing the buprenophine nasal spray

composition of Eriksen et al. in order to incorporate chitosan and HPMC as taught by Koochaki, to modify the pH as taught by Koochaki, to incorporate the composition into a spray device, and to administer the composition in a method of inducing analgesia to arrive at the instantly-claimed invention.

34. The person of ordinary skill in the art would have been motivated to incorporate the mucoadhesives of Koochaki into the solution of Eriksen et al. because, as taught be Watts et al., this would improve retention of the drug in the nasal cavity after administration, thus improving the duration of the desired plasma concentration of the active agent (see above). The person of ordinary skill in the art would not even need to look to Watts et al. for motivation because it is very well known in the art that increasing the retention of an active compound in the nasal cavity that is administered intranasally will improve the time that the compound is available to be absorbed in the body. The person of ordinary skill in the art would have expected success absent evidence to the contrary because chitosan and HPMC are routinely used pharmaceutical excipients that would be expected to be compatible with buprenorphine.

35. Claims 19 and 60-66 are rejected under 35 U.S.C. 103(a) as being unpatentable over Eriksen et al. (Applicant-cited reference on IDS: Eriksen, J. et al. *J. Pharm. Pharmacol.* **1989**, *41*, 803-805.) in view of Williams et al. (Applicant-cited reference on IDS: WO 02/00195 A2, January 3, 2002).

36. Eriksen et al. teach the composition comprising dextrose and 2 mg/ml buprenorphine as buprenorphine hydrochloride, as well a method of preparing said

composition, a nasal spray device for intranasal administration of said composition, and a method of inducing analgesia comprising intranasally administering said composition, as discussed above.

37. Eriksen et al. do not teach the compositions as further comprising chitosan and polyoxyethylene-polyoxypropylene copolymers, or the pH of the solution as being from 3 to 4.8.

38. Williams et al. teach, "A composition comprising a mucoadhesive, a local anesthetic or a pharmaceutically-acceptable salt thereof, and an opioid or a pharmaceutically-acceptable salt thereof." (claim 1; Examples 1 and 2). Williams et al. further teach, "the mucoadhesive is a block polymer of ethylene oxide and propylene oxide." (Claim 6 and p. 7, line 10 –p. 8, line 11). Williams et al. teach, "Preferably, the pH of the composition is within the range of from about 2 to about 9, more preferably, about 3 to about 7, even more preferably about 4 to about 5, and optimally about 4.5." (p. 10, lines 26-30).

39. It would have been obvious to a person of ordinary skill in the art at the time of invention to modify the procedure for preparing the buprenophine nasal spray composition of Eriksen et al. to incorporate the mucoadhesives of Williams et al. into the solution taught by Eriksen et al., to modify the pH as taught by Williams et al., to incorporate the composition into a spray device, and to administer the composition in a method of inducing analgesia, to arrive at the instantly-claimed invention.

40. The person of ordinary skill in the art would have been motivated to incorporate the mucoadhesives of Williams et al. into the solution of Eriksen et al. because, as

taught be Watts et al., this would improve retention of the drug in the nasal cavity after administration, thus improving the duration of the desired plasma concentration of the active agent by increasing retention of the agent in the nasal cavity (see above). As discussed above, the person of ordinary skill in the art would not need Watts et al. because the utility and purpose of nasal spray solutions for delivering pharmaceuticals is well-recognized in the art. The person of ordinary skill would have further been motivated with a reasonable expectation of success because Williams et al. teach that buprenorphine is a suitable opioid for incorporation into compositions containing the specified mucoadhesives for intranasal delivery (p. 4, lines 11-26).

Double Patenting

41. A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefor ..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. See *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the conflicting claims so they are no longer coextensive in scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

42. Claims 1-10, 12-16, 19, 56-59, and 63 are provisionally rejected under 35 U.S.C. 101 as claiming the same invention as that of claims 16, 19, 35, 36, 38-43, 45-47, and 49-56 of copending Application No. 10/508,315. This is a provisional double patenting rejection since the conflicting claims have not in fact been patented.

43. The indicated claims of '315 teach the identical compositions comprising buprenorphine with pectin, chitosan and hydroxypropylmethylcellulose, or chitosan and polyoxyethylene-polyoxypropylene copolymer, and methods of making and using said compositions as the indicated claims of the current application.

44. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., In re Berg, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); In re Goodman, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); In re Longi, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); In re Van Ornum, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); In re Vogel, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and In re Thorington, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

45. Claims 11, 38, 39, 41, 48-55, 60-62, and 64-66 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-56 of copending Application No. 10/508,315. Although the conflicting claims are not identical, they are not patentably distinct from each other because they are drawn to obvious variants of the same subject matter.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

46. Claim 48 of '315 teaches, "An aqueous solution suitable for intranasal administration, which comprises 0.1 to 10 mg/ml of buprenorphine or a physiologically acceptable salt or ester thereof and from 5 to 40 mg/ml of a pectin having a degree of esterification of less than 50%; which solution has a pH of from 3 to 4.2, is substantially free from divalent metal ions and gels on the nasal mucosa," said composition having an osmolality of from 0.25 to 0.4 osmol/kg.

47. '315 does not teach the solution as having an osmolality of from 0.35 to 0.5 osmol/kg.

48. It would have been obvious to a person of ordinary skill in the art at the time the invention was made to adjust the osmolality to within a range that is considered suitable within the art for intranasal delivery. Furthermore, the small change of the osmolality range does not constitute a patentably distinct composition because it does not alter the properties of the compositions with respect to their intended use.

49. Claims 53-54 of '315 teach a nasal delivery device, and more specifically a spray device, which is loaded with the composition of claim 16 of '315, namely, "An aqueous solution suitable for intranasal administration, which comprises: (a) from 0.1 to 10 mg/ml of buprenorphine or a physiologically acceptable salt or ester thereof, (b) from 0.1 to 20 mg/ml of a chitosan, and (c) from 0.1 to 15 mg/ml of hydroxoropylmethylcellulose; which solution has a pH of from 3 to 4.8."

50. '315 does not teach a nasal delivery device, or a nasal device which is a spray device, loaded with the composition of claim 38 of '315, which is the same composition as claim 1 of the instant application.

51. It would have been obvious to a person of ordinary skill in the art at the time invention was made to put the composition of claim 38 of '315 into the same nasal delivery device taught in claims 53-54 of '315 for administering the composition of claim 16 of '315 to make the invention of claims 38-39 of the instant application.

52. The person of ordinary skill in the art would have been motivated to put the composition of claim 16 of '315 into the nasal delivery device or spray device taught in claims 53-54 of '315 because it would allow them to deliver the same active agent, buprenorphine, in the same method of inducing analgesia, and would have expected success absent evidence to the contrary.

53. Claim 56 of '315 teaches a method of inducing analgesia which comprises intranasal administration of the composition of claim 16 of '315.

54. '315 does not teach a method of inducing analgesia comprising intranasal administration of the composition of claim 38 of '315, which is the same composition as claim 1 of the instant application.

55. It would have been obvious to a person of ordinary skill in the art at the time the invention was made to use the composition taught in claim 38 of '315 in the method of inducing analgesia taught in claim 56 of '315 to make the invention of claim 41 of the instant application.

56. The person of ordinary skill in the art would have been motivated to use the composition taught in claim 38 of '315 in the method of claim 56 of '315 because they contain the same active agent, buprenorphine, and would have expected success absent evidence to the contrary.

57. Claims 1, 13, 16, 19, 38-39, 41, 56-59, and 64-66 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-2, 8, and 12 of U.S. Patent No. 6,387,917. Although the conflicting claims are not identical, they are not patentably distinct from each other because they are obvious variants of the same invention.

58. '917 teaches a composition adapted for intranasal delivery comprising a methane sulphonate salt of an opioid analgesic, and further comprising chitosan or a salt or derivative thereof (claims 1 and 2). '917 also teaches a method of treating pain comprising administering to the nose a methane sulphonate of an opioid analgesic (claim 8), and a nasal drug delivery device containing as a drug a methane sulphonate salt of an opioid analgesic (claim 12).

59. '917 does not teach use of buprenorphine in the compositions or methods as the opioid analgesic.

60. It would have been obvious to a person of ordinary skill in the art at the time of invention to generate a methane sulphonate salt of buprenorphine, put it into the composition suitable for intranasal delivery taught in '917, place the composition into the

nasal delivery device taught in '917, and use the composition in the method of treating pain taught in '917, to make the inventions the current application.

61. The person of ordinary skill in the art would have been motivated to use buprenorphine in the compositions and methods of '917 because '917 teaches compositions for intranasal administration which comprise analgesics generally, and buprenorphine is a well known analgesic that is administered intranasally. The person of ordinary skill in the art would have been further motivated because '917 states, this would "provide an increased absorption of the drug." (column 2, lines 66-67). The person of ordinary skill would have expected success absent evidence to the contrary.

Response to Arguments

62. Applicant's arguments filed May 22, 2006, have been fully considered but they are not persuasive.

63. Applicant's rebuttal arguments against the rejection under 35 USC § 102 over Eriksen et al. have been considered but are unpersuasive. Applicant specifically argues that Eriksen et al. do not anticipate the instantly claimed composition because the therapeutic plasma concentration achieved by the composition of Eriksen et al. falls to 0.34 ng/ml in 4 hr and to 0.23 ng/ml at 6 hr. As discussed above, the therapeutic concentration disclosed by Eriksen et al. of 0.44 ng/ml at 3 hr after administration anticipates the instantly claimed maintained concentration levels of 0.4 ng/ml for up to 6 hr or from 2 to 4 hours.

64. Applicant's rebuttal arguments against the rejection under 35 USC § 103 as being unpatentable over Eriksen et al. in view of Watts et al., Reich et al. and Nairn are unpersuasive. Specifically, Applicant argues that the combined references do not suggest the instant compositions because there is not teaching of the presence of dextrose and absence of pectin with a DE of less than 50%, or of a pH of 3-4.2, or of the absence of divalent cations, or of the fact that the formulations gel on the nasal mucosa. First, as was stated in the previous Office Action, Eriksen et al. teach incorporation of **dextrose** (see p. 803 of Eriksen et al.). As was stated in the previous Office Action, Watts et al. teach incorporation of pectins with a DE of less than 50%. Watts et al. exemplify a composition comprising a pectin with a DE of less than 50% with a pH of 4.01 (within the herein claimed range) that gels on the nasal mucosa when the concentration of the pectin is greater than 4 mg/ml (see Table 1 in Example 1).

65. Applicant further argues that the combined references do not suggest a rapid onset of analgesia, a closer to optimum level of analgesia, or analgesia that is well sustained. There arguments are unpersuasive. First, it is noted that these are limitations that are not in the claims. Applicant also asserts that one must assume that tap water was used in the formulation of Eriksen et al., and because tap water contains divalent metal ions, the instant limitation that the compositions are substantially free of divalent metal ions has not been met. The Examiner respectfully points out that a key factor in determining obviousness under § 103 is "the level of ordinary skill in the pertinent art". If the standard of the § 103 rejection was what would have been obvious to a person of no skill in the art, it might have been assumed that tap water could be used in the

formulations of Eriksen et al., and thus the instantly claimed compositions that are substantially free of divalent metal cations would not be obvious in view of Eriksen et al. However, it is very well known and routine to use deionized or distilled water in scientific experiments where the presence of metal ions or other contaminants might interfere with the results, particularly for something as sensitive as a pharmaceutical formulation.

66. Applicant finally argues that Watts et al. teach away from a formulation with the desired properties of a rapid onset of analgesia, a closer to optimum level of analgesia, or analgesia that is well sustained because Watts et al. teach that if the formulation is for local administration, the formulation should not enhance transmucosal absorption, and if for systemic administration, the formulation should retard absorption. First, it is noted that these are not limitations in the claims. Second, it is pointed out that on p. 3, lines 16-25, Watts et al. teach that incorporation of the pectins into nasal spray solutions produces a simple nasal delivery system that can be used to modify (increase or decrease) the absorption characteristics when administering drugs systemically or locally. Watts et al. teach that when the drugs are to be administered locally, the system should not enhance absorption to effect increased systemic delivery. However, this is only one of the options for modulating the absorption characteristics, and it is particularly only relevant to local delivery of the drugs. Because buprenorphine is for systemic delivery, it would have been obvious to a person of ordinary skill in the art that the pectin gelling agents could be used to increase systemic delivery of the active compounds, if desired. Also, at the Applicant-cited passage p. 14, lines 13-18, Watts et al. teach that the nasal composition can be formulated to alter (increase or decrease)

the rate of transport in the general circulation, not only decrease as Applicant asserts. See also p. 14, lines 20-24, where Watts et al. teach that the "invention may thus be used for the modification of the systemic absorption of mucosally administered drugs." Also on p. 14, Watts et al. suggest that the formulation can be used for delivery of apomorphine and fentanyl, which are systemic analgesics similar to buprenorphine. Finally, it is noted that Applicant's stated objective of a well sustained analgesia is achieved by the teaching of Watts et al. that, as Applicant states, "Watts is entirely towards....sustained release of a drug to the nasal mucosa." This was in fact the motivation stated in the previous Office Action to combine Watts et al. with Eriksen et al.

67. Applicant's rebuttal arguments against the rejection under 35 USC § 103 as being unpatentable over Eriksen et al. in view of Koochaki are unpersuasive. Applicant argues that the combined references do not teach the presence of dextrose and the absence of chitosan and HPMC, or a pH of 3-4.8. As stated in the previous Office Action and above, Eriksen et al. teach incorporation of dextrose. It is noted that claim 16 is drawn to a composition comprising buprenorphine, chitosan, and HPMC, not buprenorphine and pectin. Thus, Koochaki suggests incorporation of the claimed additives, chitosan and HPMC. As stated in the previous Office Action, Koochaki exemplifies a composition with a pH of about 4.5, which is within the instantly claimed range (Example 1). Thus, no limitations are unaddressed.

68. Applicant's rebuttal arguments against the rejection under 35 USC § 103 as being unpatentable over Eriksen et al. in view of Williams et al. are unpersuasive. Applicant's argument regarding the presence of dextrose has been addressed. It is

noted that claim 19 is drawn to a composition comprising buprenorphine, chitosan, and polyox, not buprenorphine and pectin. Thus, Williams et al. suggest incorporation of the herein-claimed additives chitosan and polyox. As stated in the previous Office Action, Williams et al. teach that 4.5, which is within the instantly claimed range, is an optimal pH for formulations comprising chitosan and polyox.

69. Applicant's rebuttal arguments against the double-patenting rejection over Illum et al. (US 6,387,917) have been considered but are unpersuasive. Applicant argues that Illum is drawn to compositions for parenteral or non-parenteral administration of a systemically acting opioid analgesic in which the anion enhances absorption of the drug and that there is no teaching of formulations for the nasal cavity that comprise buprenorphine, or that buprenorphine should be selected from the general opioids. Claim 1 of Illum et al. states that the composition is intended for nasal delivery of a methanesulphonate salt of an analgesic. Applicant acknowledges in the arguments that the compositions are for "administration of a systemically acting opioid analgesic". Buprenorphine is a well-known, systemically acting opioid analgesic that is administered intranasally (see Eriksen et al.). The person of ordinary skill in the art would expect that the methanesulphonate salt of buprenorphine could be used with the composition comprising chitosan taught by Illum et al., or with any other known excipients for intranasal formulation, such as those taught by Watts et al., Koochaki, or Williams et al., which are discussed above. Thus, the instantly claimed invention is obvious in view of Illum et al. and the state of knowledge in the art.

70. No arguments are seen to be unaddressed.

Conclusion

71. No claims are allowed.

72. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kevin J. Capps whose telephone number is (571) 272-8646. The examiner can normally be reached on Monday-Friday, 7:30am-5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan can be reached on (571) 272-0629. The fax phone

number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

KC

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SUPERVISORY PATENT EXAMINER